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Hormone Replacement in Women with Breast Cancer

The HABITS Study

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Ever since Professor William T. Creasman suggested the use of hormone replacement therapy in breast cancer survivors in the early 1980s, interest in this field has been guarded but present. Prescribing HRT to breast cancer survivors was initially thought of as being outrageous. Yet even then with experience in HRT spanning a good three decades, and with the breast cancer epidemic, so confidently predicted, then as it is now never actually materializing, doctors working in the field had started to question the conventional wisdom. The debate on whether to treat breast cancer survivors with HRT has been revisited from time to time as there has been a powerful demand for a solution for such symptomatic women. The HABITS study was thus designed to investigate the use of HRT in breast cancer survivors.

Key Words: HRT; HABITS study; breast cancer.

Introduction

Ever since Professor William T. Creasman suggested the use of hormone replacement therapy in breast cancer survivors in the early 1980s, interest in this field has been guarded but present *(1)*. Prescribing HRT to breast cancer survivors was initially thought of as being outrageous. Yet even then with experience in HRT spanning a good three decades, and with the breast cancer epidemic, so confidently predicted, then as it is now never actually materializing, doctors working in the field had started to question the conventional wisdom.

The drive to treat women survivors of breast cancer stemmed from the fact that HRT did benefit postmenopausal symptomatic women and improved their quality of life dramatically. Moreover, tamoxifen or tamoxifen and adjuvant chemotherapy given to these women significantly worsened symptoms related to the menopause *(2)*. Secondly, the convincing data on the positive benefits for quality of life was based on the fact that symptomatic women improved greatly and experienced benefits from HRT which, to use one of the commonest phrases heard from women themselves, "makes their lives worth living again."

The debate on whether to treat breast cancer survivors with HRT has been revisited from time to time as there has been a powerful demand for a solution for such symptomatic women. The HABITS study was thus designed to investigate the use of HRT in breast cancer survivors *(3)*.

The HABITS Study

Hormonal Replacement Therapy after Breast Cancer—Is It safe? (HABITS), a randomized comparative study, was prematurely terminated in December 2003.

In the 1990s several trials to investigate the safety of recommending HRT for menopausal symptoms in survivors of breast cancer were started *(3)*. Observational findings suggested that the risk of worsening prognosis by giving hormone replacement therapy (HRT) to breast cancer survivors was low *(1,4)*.

Centers in Scandinavia (International Breast Cancer Group) and from the European Organisation for Research and Treatment of Cancer joined the study. Recruitment was started in May 1997. Owing to slow recruitment in 2002, HABITS and a similar trial in Stockholm, Sweden agreed to pool safety and final analysis in the future. Problems arose in late 2003 when the HABITS study suspended its trial on the basis of a relative hazard for HRT compared to the non-HRT group that was significantly larger than one [relative hazard (RH) 1.8, 95% CI, 1.03–3.01] in the pooled data from the HABITS and the Stockholm trial. There were however differences between the two groups in the recurrence of breast cancer. The HABITS arm showed an RH of 3.3 (95% CI, 1.5–7.4) and the Stockholm trial showed an advantage (being able to treat symptoms without increased risk) with a RH of 0.82 (95% CI, 0.35–1.9) when HRT breast cancer survivors were compared to the non-HRT groups.

As is becoming a pattern in these sorts of studies that are suspended perhaps prematurely, actual numbers are not given adequate weight nor are carefully reasoned out explanations for the phenomena observed sought. The Stockholm trial was left in the lurch and decided to stop their trials due to inadequate patients and anticipated difficulties in recruitment and compliance.

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In the HABITS study, despite the fact that the study had been going on since 1997, 345 women had at least one follow up of the 434 women randomized by September 2003. They were a group of women on the usual range of preparations. HRT treatments ranged from estrogen to estrogen/progestagen combinations, continuous combined and sequential combinations, and even tibolone at baseline. Once started there was no specific preferred therapy and, while tibolone was not allowed, estrogen only, cyclic combined estrogen progestagen combinations, and continuous combined estrogen progestagens were allowed. Once again this is a heterogeneous group of therapies, which must render the ultimate interpretation difficult.

Participants were given HRT for 2 yr in the HRT arm and followed up by a breast cancer specialist at least twice a year for the first 3 yr of follow up in total. With only 345 women having at least one follow up, this could suggest that there were a number of women who would only have been on the trial for 6 mo (mean follow up 2.1 yr, range 0.1–5.3). The relatively large number of women who had not even returned for their final follow up check ($n = 89$) is also indicative that, first, the trial was, as the authors suggest, finding it difficult to recruit women and, second, that once the trial had started, the authors were not willing to stay the course.

Twenty-six women in the HRT group ($n = 174$) and eight women in the non-HRT group ($n = 171$) were reported to have experienced new breast cancer events. In the HRT group, 11 of these events were local recurrences, 5 were contralateral cancers, and 10 were distant metastases with 2, 1, and 5, respectively, in the non-HRT group. Given these figures and the current climate, one can understand the nervousness felt by the study group. What is interesting, however, is the mortality rate. Despite the perceived increase in number of cases, five women died from a cause other than breast cancer, three due to breast cancer, and one alone to an unknown cause. Even assuming that the woman dying from an unknown cause died from breast cancer, this number is exactly the same (four) as the four that died in the non-HRT group, where all died from breast cancer.

There is not enough data to explain why the HABITS data and the Stockholm data differed, and this unique opportunity has now been lost. As has been the case in the recent history of HRT, ambitious projects are embarked upon that are perhaps over ambitious, expensive, and, because of their size and design, become unwieldy and subject to inherent flaws. They are then either prematurely stopped, or results released in a piecemeal fashion (WHI study). This prevents a full global picture from being appreciated. As in the case of the WHI, it is only now, some years after part of the original data was released, that we have access to the Premarin-only arm of the study, and the results are reassuring despite the population of women studied being older than the normal group on HRT.

In the case of the HABITS study the women will continue to be followed after study termination. However, the real problems with the study were, one suspects, organizational ones. From the start it was difficult to recruit suitable women and to have compliance. Hence, a heterogeneous group was recruited. Once the study group did not stay the course with the study, despite reassuring breast cancer mortality figures, the plug was pulled out and we are left none the wiser.

Our recommendation is that we go back to our cell biology studies and give these studies their deserved prominence. Then and only then, when we are on much safer ground, should we embark on studies of HRT in breast cancer survivors.

In the meantime, as usual, the actual recommendations have to be left to the people on the ground. Namely, there is very weak, if any, evidence to suggest that the use of HRT in breast cancer survivors, particularly in those who have had their disease diagnosed 5 yr previously and have responded well to treatment, is going to compromise their ultimate prognosis. From the Million Women Study, WHI, and others, the suggestion is that this is even more so if women are on estrogen only. Estrogen actually has the effect of potentiating cytotoxic agents that the women might have been on, including possibly tamoxifen. Such cases have to be carefully selected and should be ones where there are clear short-term benefits in terms of menopausal symptom relief.

Discussion

A profound paradox exists where women who have developed breast cancer have more favorable outcomes after utilizing HRT post-breast cancer. Several studies indicate a reduced mortality for breast cancer in women who have had HRT post treatment for breast cancer. The largest cohort study to date, the Nurses' Health Study, indicates a reduction in mortality from breast carcinoma in nurses having had HRT after breast cancer *(1)*. Another large study, the Iowa Women Health Study, showed an adjusted RR for total mortality in women with a family history of breast cancer who were currently on HRT for more than 5 yr of 0.55 (CI, 0.28–1.07), which was not different from women without a family history of breast cancer *(5)*. A longitudinal retrospective observational study carried out by five Sydney doctors between 1964 and 1999 recruited 1122 women followed up for 0–36 yr (median 6.08 yr). Two hundred and eighty six women used HRT for up to 26 yr (median 1.75 yr). Compared to non-users, HRT users had a reduced risk of cancer recurrence (RR 0.62, CI 0.43–0.87) and death from primary tumours (RR 0.40, CI 0.22–0.72) *(6)*.

Women who developed breast cancer following HRT have been noted to have cancers more amenable to treatment. The breast cancers in these women were noted to be smaller in size (5). Moreover, these tumors appeared less

aggressive, better differentiated with low cellular proliferation (Iowa study) *(5)*. Progestagens have been shown to reduce estrogen receptor production, reduce the expression of various growth factors and induce apoptosis *(7)*. This may partially explain the findings of a number of retrospective studies whereby very low recurrence and death rates were noted in women having HRT post-breast cancer *(8,9)*. These have been followed by larger case control studies again indicating similar findings. DiSaia et al. identified 125 breast cancer cases who had HRT after being treated for their breast cancer. These were matched with 362 women with breast cancer who did not utilize HRT *(10)*. The odds ratio for mortality was 0.28 (CI, 0.11–0.71) in the estrogen users significantly lower than the nonuser group ($p < 0.01$) *(10)*.

Another case control study reviewed the medical and pharmacy records of 2755 women with breast cancer. A total of 174 women were found to have used HRT after breast cancer. The recurrence rate in the estrogen users was 17/1000 person years, while the nonuser rate was 30/1000 person years (RR = 0.50, CI, 0.30–0.85). Mortality rates followed the same pattern with the estrogen user rate being 5/1000 person years and the non-estrogen-user mortality rate being 15/1000 person years (RR = 0.34, CI, 0.13–0.91) *(4)*.

Estrogen itself had been used in high doses as an anti-breast-cancer treatment for many years. Also, estradiol in cell culture was often used as one of the drugs of choice in cytotoxic cell trials. Thus, for example, tamoxifen would be tested for efficiency on breast cancer cell lines against estradiol and some recent new agents would be tested against estradiol and tamoxifen with estradiol being an effective cytotoxic agent in such breast cancer cell lines. More recent studies are utilizing cytotoxic linked to estrogens, which bind to estrogen receptors and thereby deliver the cytotoxic effect in a more concentrated form to tumor cells *(11)*.

One other study indicates that pretreatment with 17β-estradiol improved the efficacy of the cytotoxic agent doxorubicin on MCF-7 human breast cancer cells. This study suggested that estrogenic pretreatment is a potential tool for enhancing cytotoxic activity of doxorubicin *(12)*.

Encouraging results have also been shown for the comparison of tamoxifen and estrogen in post-breast-cancer patients. A similar response to tamoxifen was noted in women taking HRT following breast cancer. Moreover, in some studies the median survival time was considerably longer, one study indicating a survival time of 13.5 mo more in the estrogen user group compared to the tamoxifen group *(13)*.

Tamoxifen does have cytotoxic benefits for breast cancer treatment in women with estrogen-receptor-negative breast cancer as well as the more obvious receptor-positive ones. This suggests that in addition to an estrogen receptor mode of action there is also some other as yet poorly defined mode of action of tamoxifen on breast cancer. In one study, women who have taken concomitant tamoxifen with combined continuous estrogen–progesterone therapy achieved a hazard ratio of 0.67 (95% CI, 0.14–3.24), $p = 0.62$. The hazard ratio for estrogen users who were estrogen receptor positive was 0.24 (95% CI, 0.1–1.4), $p = 0.14$ *(14)*.

Most women who develop breast cancer will undergo chemotherapy. The vast majority will develop a chemotherapeutically induced amenorrhea and menopause. Similar to a surgical menopause, this menopause will result in severe vasomotor symptoms over a longer period of time compared to a natural menopause. Moreover, the long-term effects such as postmenopausal osteoporosis and cardiovascular disease may be expected to occur with greater severity similar to a surgical menopause.

The improved quality of life and increased longevity by postmenopausal women using HRT/ERT has been alluded to by a number of important institutions *(15,16)*. The positive impact may be due to a multiplicity of variables, which in concert increase the positive influence of HRT/ERT. Variables, which require further examination, are the interaction of estrogen status, genetic polymorphisms and their influence on the body's natural immunological surveillance *(17)*. This may be a key factor in deciding on the appropriate administration of HRT/ERT to women especially those women who have had breast cancer in the past.

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